REMARKS

Upon entry of the above amendment, claims 40-42, 49, 50, 54, and 59 will be pending in the application, claims 55 and 58 having been newly canceled without prejudice. The amendments to claims 40, 41, and 59 are generally supported in the specification, e.g., at page 2, lines 14-15; and page 26, line 16, to page 27, line 17. Newly canceled claims 55 and 58 were withdrawn by the Examiner as being directed to a nonelected invention. Applicants maintain the right to pursue the subject matter of the canceled claims in a divisional application.

On the "Office Action Summary" page included at the beginning of the Office action, the category "Priority under 35 U.S.C. § 119" contains no indication that the priority documents were received by the Office from the International Bureau in this National Stage application. Acknowledgement that the documents were received is requested, so that the record is clear on this point.

Applicants thank the Examiner for withdrawing the prior grounds for rejection.

All of the presently pending claims have been rejected on a new ground: obviousness under 35 USC § 103(a) in view of WO 2002/033072 A1 (a Japanese publication) as evidenced by the US national phase application US 2004/0091475 (in English). To the extent that the rejection may be applied to the claims as presently amended, it is respectfully traversed.

In the discussion below, Applicants will follow the Examiner's lead in referring to paragraph and page numbers of US 2004/0091475.

Independent claims 40 and 41 of the present application both contain similar limitations, differing in the description of the "TPO-like agonistic activity" specified in the preamble of each claim and referenced in parts (d) and (e), and in the reference to either "covalently linked scFv multimer" (in claim 40) or "single-chain antibody" (in claim 41). Claim 40, as amended, reads as follows:

> **40. (Currently amended) A method for selecting a scFv multimer with thrombopoietin (TPO)-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor, the method comprising**

(a) identifying an antibody that binds to mpl receptor;

(b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence;

(c) producing a covalently linked scFv multimer comprising two copies of said light chain variable region sequence of (b) and two copies of said heavy chain variable region sequence of (b), linked via linkers;

(d) testing the covalently linked scFv multimer for said TPO-like agonistic activity;

(e) demonstrating that the covalently linked scFv multimer binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b); and

(f) selecting the covalently linked scFv multimer.

Amended claim 41 reads:

41. (Currently amended) A method for selecting a single-chain antibody with TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating mpl receptor, the method comprising

(a) identifying an antibody that binds to mpl receptor;

(b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence;

(c) producing a single-chain polypeptide comprising two or more copies of the light chain variable region sequence of (b) and two or more copies of the heavy chain variable region sequence of (b), linked via linkers;

(d) testing the single-chain polypeptide for said TPO-like agonistic activity;

(e) demonstrating that the single-chain polypeptide binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the

level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b); and

(f) selecting the single-chain polypeptide.

Amended independent claim 59 is similar to amended claim 41, except that parts (c) and (e) of claim 59 specify a "humanized version" of the light and heavy chain variable region sequences.

According to the Office action at pages 6-8,

WO 2002/033072 A1 teaches methods comprising

(a) identifying an antibody that binds to mpl receptor;
(b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence;
(c) producing an sc(Fv)$_2$ or covalently linked scFv multimer comprising two or more copies of said light chain variable region sequence of (b) and two or more copies of said heavy chain variable region sequence of (b), linked via linkers; and
(d) testing the sc(Fv)$_2$ or covalently linked scFv multimer for said TPO-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor.

The Office action goes on to acknowledge that

WO 2002/033072 A1 does not expressly teach (e) selecting the sc(Fv)$_2$ or covalently linked scFv multimer if it binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b).

In other words, the Office action acknowledges that the cited reference does not disclose parts (e) and (f) of any of the present independent claims, as amended. The Office action attempts to make up for this deficiency by asserting at page 8 that "*it would have been prima facie obvious*

to one of ordinary skill in the art at the time the claimed invention was made based on the disclosed motivation of preferably selecting a modified antibody with higher TPO agonist activity." To support this alleged motivation, the Office action points to the language at pages 1 and 2 of the cited reference regarding making and testing modified antibodies that have TPO agonist action. The Office action also finds motivation to "select" the modified antibody "*since WO 2002/033072 A1 clearly teaches a preference for antibodies and having higher TPO agonist action as compared to another antibody having TPO agonist action.*" Furthermore, the Office action at page 8 opines that one of skill in the art would have had an expectation of success:

> *Finally, since WO 2002/033072 A1 clearly teaches testing and screening steps that monitor modified antibodies for TPO-like agonistic stimulation of cell proliferation one of skill in the art also would have had a reasonable expectation of success in practicing methods encompassed by the claims.*

Applicants respectfully disagree that WO 2002/033072 A1 supplies either a motivation to carry out the presently claimed methods or an expectation of success upon doing so. Each of the independent claims (as amended) requires production of a covalently linked scFv multimer, testing it for TPO-like agonistic activity, and demonstrating that it binds to mpl receptor and exhibits greater activity than is exhibited by either the parental antibody or a two-chain diabody sharing the same variable domain sequences. While WO 2002/033072 A1 does generally disclose the idea of making single chain polypeptides containing two or more H chain V regions and two or more L chain V regions (see, e.g., [0013] of US 2004/0091475 A1)), the only modified anti-mpl antibodies actually made and tested in the reference's Examples are scFv monomers and non-covalently linked multimers of scFv, i.e., diabodies, triabodies and tetrabodies. See Examples 7 and 8 on pages 20-26 of US 2004/0091475 A1. Example 7 discloses experiments with anti-mpl antibody 12B5 and certain modified versions thereof: Fab, single-chain 12B5 monomer, and non-covalently linked single-chain 12B5 dimer (i.e., a diabody). See section 7.6 of Example 7 and Figs. 51 and 52 of US 2004/0091475 A1. Example 8 discloses experiments with another anti-mpl antibody, 12E10, and certain modified versions thereof: Fab, scFv with a 5 amino acid linker ("db12E10"), scFv with a 15 amino acid linker ("sc12E10"), non-covalently linked dimers and trimers of db12E10, and non-covalently

linked dimers of sc12E10. See section 8.6 of Example 8 and Figs. 58 and 59. In no case does WO 2002/033072 disclose test results with a sc(Fv)2 or any other covalently linked scFv multimer of any anti-mpl antibody. In fact, there is no indication that this type of modified anti-mpl antibody was ever prepared. Figs. 52 and 59 reveal that, in both cases, diabodies (i.e., two non-covalently linked scFv) were the most active form of antibody tested, and were even more active than TPO itself. There is no reason whatsoever to assume that another form of modified antibody—one that the WO 20002/033072 A1 researchers did not even bother to make—would exhibit even greater activity than the diabodies of Examples 7 and 8. Accordingly, until Applicants carried out their experiments, there could not have been an expectation that the presently claimed methods would be successful.

As further evidence that one of ordinary skill in the art would not have had an expectation of success regarding the presently claimed methods, Applicants note the experiments with anti-IAP antibodies MABL-1 and MABL-2 discussed in Examples 1-6 of WO 2002/033072 A1. (IAP stands for "Integrin Associated Protein.") These antibodies are capable of inducing apoptosis of IAP-expressing cells (see [0005] of US 2002/0091475 A1). Example 6 on page 15 of US 2002/003072 A1 discloses production of a covalently linked scFv dimer of MABL-2. See the schematic drawing of a vector shown in Fig. 34. When the apoptotic activity of this covalently linked scFv dimer (termed "MABL2-sc(Fv)$_2$") was compared to the apoptotic activity of a MABL-2 diabody (termed "MABL2-scFv <HL-5>") in two different cell lines, the diabody was shown to be more active than the covalently linked scFv dimer in both kinds of cells. See Fig. 43. These experiments teach that, in the context of an antibody that cross-links a molecule on the surface of a cell, a diabody form of the antibody is more active than a covalently linked scFv dimer form of the same antibody. One of ordinary skill would generally expect the same to be true of other antibodies that act on other cell-surface molecules. The reference provides no basis whatsoever to assume the inverse would be true in the case of an anti-mpl antibody. Thus, all of the prior art evidence of record supports the conclusion that one of ordinary skill in the art would not have had a reasonable expectation of success in carrying out the presently claimed

methods. Absent a reasonable expectation of success in the art, there is no *prima facie* obviousness, and the rejection must fail on that ground alone.

Furthermore, the fact that one of ordinary skill in the art would not have reasonably expected the claimed methods to be successful suggests that there would have been no reason—i.e., no motivation—to carry out the methods as claimed. The evidence in Example 6 of the cited reference teaches that a diabody is more active than its counterpart covalently linked scFv dimer, so *teaches away* from the presently claimed methods. Applicants submit that the obviousness rejection fails on this ground—lack of motivation—as well.

Withdrawal of the rejection and allowance of the claims are respectfully requested. If any issues remain, the Examiner is asked to telephone the undersigned so that they can be expeditiously resolved.

The fee in the amount of $1,110.00 for a Petition for Three Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-0164US1.

Respectfully submitted,

Date: Oct. 15, 2010

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